Efficacy of extended thrombo-prophylaxis in major abdominal surgery. What does the
evidence show: a meta-analysis.

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CRD summary
The authors concluded that extended thromboprophylaxis with low molecular weight heparin should be considered a safe and useful method for the prevention of venous thromboembolism in high-risk major abdominal surgery. This was generally a well-conducted review and the authors’ conclusions were likely to be reliable.

Authors’ objectives
To compare the safety and efficacy of extended thromboprophylaxis (ETP) with conventional in-hospital prophylaxis in patients undergoing major abdominal surgery.

Searching
MEDLINE, EMBASE, LILACS, the Cochrane Library, Cochrane Controlled Trials Register and the registry of the United States National Institutes of Health were searched from inception to February 2007. Search terms were reported. No language restrictions were applied. In addition, abstracts of four specified relevant meetings (2000 to February 2007) and references of identified studies, reviews and guidelines were screened. Manufacturers of antithrombotic agents were contacted and national and international experts consulted for additional studies.

Study selection
Randomised controlled trials (RCTs) and controlled clinical trials that compared an ETP regimen (for at least 21 days after surgery) with the same regimen limited to the in-hospital period in adults (aged >18 years) undergoing major abdomino-pelvic surgery were eligible for inclusion. Details of eligible ETP regimens were specified in the review. Studies had to objectively assess venous thromboembolism (VTE) at the end of the observation period, assess thromboembolic events using any of the specified methods and adequately report bleeding events and mortality. In addition, studies had to be double-blinded or open with blinded outcome assessment and score more than 2 on the Jadad scale.

The included studies evaluated low molecular weight heparin (LMWH, tinzaparin, dalteparin and enoxaparin) with or without elastic stockings; the duration of ETP regimens ranged from 25 to 31 days. All studies randomised patients post-operatively. Most patients (71 per cent) underwent surgery for cancer. The median age was 67 years (range 22 to 93 years). All studies evaluated VTE using lower limb bilateral venography (after a mean of 32 days post surgery). The review also included some patients who had undergone non-cardiac thoracic surgery, since they could not be separated from the group of interest. The duration of follow-up was 28 days or three months.

Two reviewers independently selected studies. Discrepancies were resolved through discussion with the aid of a third reviewer if required.

Assessment of study quality
Two reviewers independently assessed validity using the Jadad scale (reporting of randomisation, blinding and withdrawals). The maximum possible score was 5. Discrepancies were resolved through discussion with the aid of a third reviewer if required.

Data extraction
The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction. Intention-to-treat (ITT) data were used for efficacy end points and per-protocol data used for safety outcomes.

Methods of synthesis
Pooled relative risks (RR) and 95% confidence intervals (CI) were calculated using a fixed-effect model. Reductions in relative risk and number needed to treat (NNT) were calculated for statistically significant findings. Heterogeneity was
assessed using the Q-statistic, the $I^2$ statistic and a Galbraith plot. Sensitivity analysis was undertaken by analysing cancer patients separately; it was not clear if this analysis was specified in advance or was a post hoc decision. Publication bias was assessed using the Begg and Egger tests.

**Results of the review**

Three RCTs were included (n= 1,104). All three studies scored 3 or more out of 5 on the Jadad scale. One study was double blinded; the other two were open-label with blinded outcome assessment.

Compared to in-hospital prophylaxis, ETP was associated with a statistically significant reduction in VTE, 5.93 per cent versus 13.6 per cent, RR 0.44 (95% CI: 0.28, 0.7), deep vein thrombosis (DVT), 5.93 per cent versus 12.9 per cent, RR 0.46 (95% CI: 0.29, 0.74) and proximal DVT, 1.0 per cent versus 4.72 per cent, RR 0.24 (95% CI: 0.09, 0.67). NNT was 13 (95% CI: 8.5, 28) for VTE, 14.5 (95% CI: 9, 34.5) for DVT and 27 (95% CI: 16.67, 71.92) for proximal DVT. Few patients had symptomatic VTE.

There were no statistically significant differences between ETP and in-hospital prophylaxis in major and minor bleeding or mortality. There were only five episodes of pulmonary embolism, all in control groups.

No significant heterogeneity was found. There was moderate heterogeneity for major bleeding ($I^2$ 54 per cent). There was no evidence of publication bias (Egger and Begg tests were not statistically significant).

**Authors' conclusions**

Extended thromboprophylaxis with LMWH should be considered a safe and useful method for the prevention of venous thromboembolism in high-risk major abdominal surgery.

**CRD commentary**

The review question was clearly stated and inclusion criteria were defined. Several relevant sources were searched and attempts were made to minimise publication and language bias. The potential for publication bias was assessed, but this was of limited value due to the small number of studies. Methods were used to minimise reviewer errors and bias in the selection of studies and assessment of validity, but it was not clear whether similar steps were taken during data extraction. Only RCTs were included, validity was assessed and results were reported. Appropriate methods were used for the meta-analyses. Heterogeneity was assessed. The small number of events in some analyses may reduce the strength of the findings. This was generally a well-conducted review and the authors’ conclusions were likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors recommended that a cost-effectiveness study be considered to compare extended thromboprophylaxis with conventional therapy in patients undergoing major abdominal surgery.

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